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(54) Title: NASAL FORMULATION OF AN ANTIFUNGAL

(57) Abstract: The present invention concerns novel formulations comprising an antifungal agent having a low solubility in aqueous media, a process for preparing said formulations and pharmaceutical dosage forms comprising said novel formulations for nasal administration.

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NASAL FORMULATION OF AN ANTIFUNGAL

The present invention concerns novel formulations comprising an antifungal agent having a low solubility in aqueous media, a process for preparing said formulations and pharmaceutical dosage forms comprising said novel formulations for nasal administration.

Formulations containing antifungals can be administered intranasally to treat patients suffering from fungal inflammations or fungal infections, more in particular fungus-associated mucosal conditions and fungal asthma. The development of efficacious aqueous pharmaceutical compositions of antifungals is often hampered considerably by the fact that they are often only very sparingly soluble in water.

The solubility of the antifungals can be increased by formulating them in an extremely acidic medium, e.g. a medium of pH 1.5.

Alternatively, the solubility may also be increased by adding a significant amount of a co-solvent, such as PEG 400, propylene glycol, glycerol, to the aqueous formulation. WO 99/20261 discloses an aqueous formulation of itraconazole containing 10% (v/v) of PEG 400.

In order to sufficiently increase the solubility, the effect of co-solvent and acidic pH is often combined. US-4,916,134 describes an oral formulation of a triazole antifungal comprising 60 % (v/v) glycerol and 0.05 % (w/v) 2,3-dihydroxybutanedioic acid.

The solubility of the azole antifungals can also be increased by complexation with cyclodextrins or derivatives thereof, as described in WO 85/02767 and US-4,764,604 . However, for ease of preparation or for increasing the stability (shelf life), the aqueous formulations comprising cyclodextrins have an acidic pH and contain a considerable amount of co-solvents. Hostetler et al. (Antimicrobial Agents and Chemotherapy, 1992, 36, pp. 477-480) discloses oral azole formulations in an acidic (pH 1.9-2.1) aqueous medium comprising 60 % (w/v) hydroxypropyl-β-cyclodextrin and 10 % (v/v) propylene glycol. US-5,707,975 describes a palatable itraconazole oral formulation of pH 2 containing 40 % or 60% (w/v) hydroxypropyl-β-cyclodextrin and 10 % (v/v) propylene glycol.

When administered intranasally, the aqueous antifungal formulations outlined above will cause side-effects, the severity of which will depend on the pH of and the amount of co-solvent processed in the formulation. A strong acidic pH or a high concentration of co-solvents causes irritation of the nasal mucosa and affects mucociliary function. Especially in the case of nasal washes where large volumes of irrigation solutions have to be applied, these side-effects have to be avoided.

The present invention concerns a formulation for nasal administration comprising an antifungal and a sufficient amount of a cyclodextrin or a derivative thereof characterized in that the bulk liquid carrier of said formulation is an aqueous buffered solution having a pH ranging from 6.0 to 8.0. By buffering the bulk carrier close to neutral pH, the tolerability of the nasal formulation is increased, which promotes patient compliance.

The formulation according to the present invention is suitable for treating patients suffering from fungal inflammations or fungal infections, particularly for treating patients with fungus-associated mucosal conditions, such as fungal sinusitis, fungal rhinosinusitis, allergic fungal sinusitis, fungus balls in the sinuses, fungal asthma, fungus-induced bronchial pulmonary allergy. The formulations of the present invention are preferably topically, more in particular intranasally, administered to treat the above mentioned conditions.

Suitable antifungals in the present invention are itraconazole, saperconazole, ketoconazole, fluconazole, miconazole, clotrimazole, voriconazole, econazole, isoconazole, bifonazole, lanoconazole, sertaconazole, orconazole, doconazole, parconazole, elubiol, terconazole, butoconazole, oxiconazole, sulconazole, flucytosine, amphotericine B, SCH-39304, SCH-42427, SCH-42538, SCH-45012, SCH-51048, UR-9746, UR-9751, UK-109496, (2S-cis)-1-[4-[4-[4-[[4-(2,4-difluorophenyl)-4-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-2-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-3-(1-methylethyl)-2-imidazolidinone, and the antifungals described in EP-A-0402989, EP-A-0631578 , EP-A-0741737 , WO 98/34934 and WO 99/02523 . The concentration of the antifungal in the formulation depends on the actual antifungal being used and the fungus that has to be tackled. The concentration of the antifungal typically ranges from about 0.001% to about 0.1% (w/v), and preferably is 0.01% (w/v).

Appropriate cyclodextrin derivatives are α-, β, γ-cyclodextrins or ethers and mixed ethers thereof wherein one or more of the hydroxy groups of the anhydroglucose units of the cyclodextrin are substituted with C_{1-6}alkyl, particularly methyl, ethyl or isopropyl; hydroxyC_{1-6}alkyl, particularly hydroxyethyl, hydroxypropyl or hydroxy-butyl; carboxyC_{1-6}alkyl, particularly carboxymethyl or carboxyethyl; C_{1-6}alkyl-carbonyl, particularly acetyl; C_{1-6}alkyloxycarbonylC_{1-6}alkyl or carboxyC_{1-6}alkyl-oxyC_{1-6}alkyl, particularly carboxymethoxypropyl or carboxyethoxypropyl; C_{1-6}alkylcarbonyloxyC_{1-6}alkyl, particularly 2-acetyloxypropyl. Especially noteworthy as complexants and/or solubilizers are β-CD, 2,6-dimethyl-β-CD, 2-hydroxyethyl-β-CD, 2-hydroxyethyl-γ-CD, 2-hydroxypropyl-γ-CD and (2-carboxymethoxy)propyl-β-CD, and in particular 2-hydroxypropyl-β-CD.

More recent examples of substituted cyclodextrins include sulfobutylcyclodextrins (US-5,134,127-A). Their use is also envisaged in the present invention.

The term mixed ether denotes cyclodextrin derivatives wherein at least two cyclodextrin hydroxy groups are etherified with different groups such as, for example, hydroxy-propyl and hydroxyethyl.

The average molar substitution (M.S.) is used as a measure of the average number of moles of alkoxy units per mole of anhydroglucose. In the cyclodextrin derivatives for use in the compositions according to the present invention the M.S. is in the range of 0.125 to 10, in particular of 0.3 to 3, or from 0.3 to 1.5. Preferably the M.S. ranges from about 0.3 to about 0.8, in particular from about 0.35 to about 0.5 and most particularly is about 0.4. M.S. values determined by NMR of IR preferably range from 0.3 to 1, in particular from 0.55 to 0.75.

The average substitution degree (D.S.) refers to the average number of substituted hydroxyls per anhydroglucose unit. In the cyclodextrin derivatives for use in the compositions according to the present invention the D.S. is in the range of 0.125 to 3, in particular of 0.2 to 2 or from 0.2 to 1.5. Preferably the D.S. ranges from about 0.2 to about 0.7, in particular from about 0.35 to about 0.5 and most particularly is about 0.4. D.S. values determined by NMR of IR preferably range from 0.3 to 1, in particular from 0.55 to 0.75.

More particular β- and γ-cyclodextrin hydroxyalkyl derivatives for use in the compositions according to the present invention are partially substituted cyclodextrin derivatives wherein the average degree of alkylation at hydroxyl groups of different positions of the anhydroglucose units is about 0% to 20% for the 3 position, 2% to 70% for the 2 position and about 5% to 90% for the 6 position. Preferably the amount of unsubstituted β- or γ-cyclodextrin is less than 5% of the total cyclodextrin content and in particular is less than 1.5%. Another particularly interesting cyclodextrin derivative is randomly methylated β-cyclodextrin.

Most preferred cyclodextrin derivatives for use in the present invention are those partially substituted β-cyclodextrin ethers or mixed ethers having hydroxypropyl, hydroxyethyl and in particular 2-hydroxypropyl and/or 2-(1-hydroxypropyl) substituents.

The most preferred cyclodextrin derivative for use in the compositions of the present invention is hydroxypropyl-β-cyclodextrin having a M.S. in the range of 0.35 to 0.50 and containing less than 1.5% unsubstituted β-cyclodextrin. M.S. values determined by NMR or IR preferably range from 0.55 to 0.75.

Nevertheless, the choice of cyclodextrin may be directed by the ability of the selected drug compound to be complexed by a particular cyclodextrin - thus the cyclodextrins with greater affinity for the particular drug compound may be preferred.

Substituted cyclodextrins can be prepared according to procedures described in US-3,459,731, EP-A-0,149,197, EP-A-0,197,571, US-4,535,152, WO-90/12035 and GB-2,189,245. Other references describing cyclodextrins for use in the compositions according to the present invention, and which provide a guide for the preparation, purification and analysis of cyclodextrins include the following : "Cyclodextrin Technology" by József Szejtli, Kluwer Academic Publishers (1988) in the chapter Cyclodextrins in Pharmaceuticals; "Cyclodextrin Chemistry" by M.L. Bender et al., Springer-Verlag, Berlin (1978); "Advances in Carbohydrate Chemistry", Vol. 12 Ed. by M.L. Wolfrom, Academic Press, New York (157) in the chapter The Schardinger Dextrins by Dexter French at p. 189-260; "Cyclodextrins and their Inclusions Complexes" by J. Szejtli, Akademiai Kiado, Budapest, Hungary (1982); I. Tabushi in Acc. Chem. Research, 1982, 15, p. 66-72; W. Sanger, Angewandte Chemie, 92, p. 343-361 (1981); A. P. Croft and R. A. Bartsch in Tetrahedron, 39, p. 1417-1474 (1983); Irie et al.

Pharmaceutical Research, 5, p. 713-716, (1988); Pitha et al. Int. J. Pharm. 29, 73, (1986); DE 3,118,218; DE-3,317,064; EP-A-94,157; US-4,659,696; and US-4,383,992.

The formulations according to the present invention typically comprise from about 0.1% to about 20% (w/v) of cyclodextrins or a derivative thereof, preferably from about 2.5% to about 15% (w/v), and more preferably about 10% (w/v).

The weight ratio of cyclodextrin to antifungal preferably ranges from about 250 to about 10,000, more preferably from 500 to 5,000, and most preferably is about 1,000.

In order to increase the rate of dissolution of the poorly soluble antifungal during the manufacturing process, an alcoholic co-solvent may optionally be employed in the formulations according to the present invention. First dissolving the antifungal in a suitable co-solvent followed by mixing this solution with an aqueous cyclodextrin medium considerably shortens and simplifies the production process. For this purpose, preference is given to those alcoholic co-solvents that have good dissolving power for the antifungals described hereinabove. Particular suitable alcoholic co-solvents are ethanol, propylene glycol, glycerol, polyethylene glycol, tetraglycol, glycofurol, with propylene glycol being preferred. Based on the total volume of the preparation, the concentration of the alcoholic co-solvent preferably ranges from about 0.01% to about 1% (v/v), more preferably from about 0.1% to about 0.5% (v/v), and most preferred is about 0.25% (v/v).

As a bulk liquid carrier there is used an aqueous buffered medium having a pH ranging from 6.0 to 8.0, preferably having a pH of 7.0. Buffering close to a neutral pH renders the nasal formulation more tolerable, it reduces irritation of the nasal mucosa and hence, it increases patient compliance.

The bulk liquid carrier of the present invention can be buffered by using a pharmaceutically acceptable buffer system, such as, for example, an acetate, citrate, carbonate, borate, phosphate, TRIS buffer, with a phosphate buffer being preferred.

The water making up the bulk liquid carrier is preferably water for injections, purified water, or demineralized water, water for injections being preferred.

In order to render the formulations of the present invention more acceptable, they may be made isotonic compared to blood (0.280 osmol/kg, freezing point depression of 0.52°C).

Typical pharmaceutically acceptable tonicity adjusting agents include sodium chloride, potassium nitrate, dextrose, mannitol, sorbitol, lactose, boric acid, sodium tartrate, propylene glycol, glycerol, and other organic and anorganic solutes. Sodium chloride is preferred, especially when combined with a sodium containing buffer system. The amount of the tonicity adjusting agents is dependent upon the concentration and the degree of dissociation of the other excipients.

The formulations can also optionally contain other additives such as one or more preservatives in order to increase the shelf life of the formulation. Pharmaceutically acceptable preservatives include quaternary ammonium salts such as lauralkonium chloride, benzalkonium chloride, benzododecinium chloride, cetyl pyridium chloride, cetrimide, domiphen bromide; alcohols such as benzyl alcohol, chlorobutanol, o-cresol, chlorocresol, phenol, phenyl ethyl alcohol, glycerol, propylene glycol; organic acids or salts and derivatives thereof such as benzoic acid, sodium benzoate, potassium sorbate, parabens, thiomersal, phenylmercuri nitrate,-borate,-acetate, chloorhexidine diacetate,-digluconate; or complex forming agents such as EDTA. The concentration of the preservative will range from 0% to 2% (w/w), depending on the actual preservative being used. In the case of nasal irrigation, preservatives are preferably omitted from the formulation as to avoid irritation, toxicity and impairment of mucociliary function associated with the application of a large volume.

An interesting formulation according to the present invention comprises by weight or volume based on the total volume of the formulation :

(a) 0.01% (w/v) itraconazole;
(b) 10% (w/v) hydroxypropyl-β-cyclodextrin;
(c) 0.25% (v/v) propylene glycol;
(d) acid to dissolve the itraconazole in combination with propylene glycol;
(e) base to adjust the pH of the formulation within the range of 6.0 to 8.0;
(f) sodium chloride to make the formulation isotonic compared to blood;
(f) $NaH_2PO_4.H_2O/Na_2HPO_4$ buffer in water for injections having a pH of 6.0 to 8.0.

The present invention also relates to a process of preparing a formulation for nasal administration comprising the steps of

(a) dissolving the antifungal in an acid, optionally in combination with an alcoholic co-solvent;
(b) dissolving the cyclodextrin in water and adding thereto the solution prepared under (a) while stirring until homogenous;
(c) adjusting the pH of the solution resulting under (b) to a pH of 6.0 to 8.0;
(d) dissolving a tonicity adjusting agent in the solution resulting under (c);
(e) diluting the formulation to the desired end-volume with an aqueous buffered medium having a pH ranging from 6.0 to 8.0.

The above general route of preparation of the formulation of the present invention may be modified by a person skilled in the art by for instance adding certain ingredients at other stages than indicated above. For example, the antifungal can also be dissolved in a solution of cyclodextrin, acid and water.

The formulation of the present invention can be provided in any pharmaceutically acceptable form suitable for being introduced into the nostrils and sinus cavities, such as nasal spray bottles, droppers, nasal irrigations, lavages or washes, nasal injections, inhalers or atomizer-type squeeze or pump bottles, all being suitable among other delivery means and being provided with suitable devices for nasal administration, such as inhalers, nebulizers, masks, syringes, sprayers, canisters, tubes. The formulation of the present invention is preferably provided in a pharmaceutically acceptable form suitable for nasal irrigation or lavage. The volume administered into the nostrils and sinus cavities preferably ranges from 0.01 ml to 100 ml per nostril, more preferably ranges from 10 to 30 ml per nostril, and most preferably is about 20 ml per nostril. The frequency of the nasal administration will typically range from about 3 to 4 times daily to only once every month, depending on the severity of the condition being treated.

The formulations of the present invention are preferably sterilized by using conventional sterilization methods, such as by heating in an autoclave, using moist heat, dry heat, filtration, ultra-violet light, radiation, gaseous sterilization. A person skilled in the art will easily recognize the most appropriate sterilization method.

A further aspect of the present invention provides the use of the above formulation as a medicine, especially the use for the manufacture of a medicament for treating patients suffering from fungal sinusitis, fungal rhinosinusitis, allergic fungal sinusitis, fungus balls

in the sinuses, fungal asthma, fungus-induced bronchial pulmonary allergy. Hence, a method of treating a patient suffering from these conditions by administering the nasal formulation of the present invention is provided.

Experimental part

Composition of the nasal antifungal formulation

0.01% (w/v) itraconazole;
10% (w/v) hydroxypropyl-β-cyclodextrin;
0.25% (v/v) propylene glycol;
0.376µl 12 N HCl;
NaOH to adjust the pH of the formulation to 7.0;
NaCl to make the formulation isotonic;
$NaH_2PO_4.H_2O/Na_2HPO_4$ buffer in water for injections having a pH of 7.0 up to 1ml.

Preparation of the nasal antifungal formulation

0.01g of itraconazole was dissolved in 250µl propylene glycol and 37.6µl 12 N HCl. 10g of hydroxypropyl-β-cyclodextrin was dissolved in water and the itraconazole solution was added while stirring until a homogeneous solution was obtained. NaOH was added to adjust the pH of the solution to 7.0. Sodium chloride was added to make the formulation isotonic compared to blood. Aqueous $NaH_2PO_4.H_2O/Na_2HPO_4$ buffer of pH 7.0 was added to bring the total volume of the formulation up to 100ml.

Claims

1. A formulation for nasal administration comprising an antifungal and a sufficient amount of a cyclodextrin or a derivative thereof characterized in that the bulk liquid carrier of said formulation is an aqueous buffered solution having a pH ranging from 6.0 to 8.0.

2. A formulation according to claim 1 further comprising an alcoholic co-solvent.

3. A formulation according to claim 2 wherein the amount of alcoholic co-solvent ranges from 0.01% to 1% (v/v).

4. A formulation according to claim 2 and 3 wherein the alcoholic co-solvent is propylene glycol.

5. A formulation according to claims 1 to 4 wherein the antifungal is itraconazole, saperconazole, ketoconazole, fluconazole, miconazole, clotrimazole, voriconazole, econazole, isoconazole, bifonazole, lanoconazole, sertaconazole, orconazole, doconazole, parconazole, elubiol, terconazole, SCH-39304, SCH-42427, SCH-42538, SCH-45012, SCH-51048, UR-9746, UR-9751, UK-109496, (2S-cis)-1-[4-[4-[4-[[4-(2,4-difluorophenyl)-4-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-2-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-3-(1-methylethyl)-2-imidazolidinone and the cyclodextrin is hydroxypropyl-β-cyclodextrin having a M.S. in the range of 0.35 to 0.50 and containing less than 1.5% unsubstituted β-cyclodextrin.

6. A formulation according to claim 5 wherein the concentration of hydroxypropyl-β-cyclodextrin ranges from 0.1% to 20% by weight based on the total volume of the formulation.

7. A formulation according to claims 1 to 6 wherein the weight ratio of hydroxypropyl-β-cyclodextrin to antifungal ranges from about 250 to about 10,000.

8. A formulation according to anyone of claims 1 to 7 having a pH of 7.0.

9. A formulation according to anyone of claims 1 to 7 comprising by weight or by volume based on the total volume of the formulation :

(a) 0.01% (w/v) itraconazole;
(b) 10% (w/v) hydroxypropyl-β-cyclodextrin;
(c) 0.25% (v/v) propylene glycol;
(d) acid to dissolve the itraconazole in combination with propylene glycol;
(e) base to adjust the pH of the formulation within the range of 6.0 to 8.0;
(f) sodium chloride to make the formulation isotonic compared to blood;
(g) $NaH_2PO_4.H_2O/Na_2HPO_4$ buffer in water for injections having a pH of 6.0 to 8.0.

10. A process of preparing a formulation as claimed in claim 1, characterized in that said process comprises the steps of :
(a) dissolving the antifungal in an acid, optionally in combination with an alcoholic co-solvent;
(b) dissolving the cyclodextrin in water and adding thereto the solution prepared under (a) while stirring until homogenous;
(c) adjusting the pH of the solution resulting under (b) to a pH of 6.0 to 8.0;
(d) dissolving a tonicity adjusting agent in the solution resulting under (c) ;
(e) diluting the formulation to the desired end-volume with an aqueous buffered medium having a pH ranging from 6.0 to 8.0.

INTERNATIONAL SEARCH REPORT

Interr ial Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/00 A61K47/40 A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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A	WO 98 55148 A (JANSSEN) 10 December 1998 (1998-12-10) claims examples 1-8	1-10
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